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β-Amyloid 42/40 ratio and kalirin expression in Alzheimer disease with psychosis

Patrick S. Murray[a,f], **Caitlin M. Kirkwood**[a], **Megan C. Gray**[a], **Milos D. Ikonomovic**[a,b,g], **William R. Paljug**[b], **Eric E. Abrahamson**[b], **Ruth A. Henteleff**[a], **Ronald L. Hamilton**[c], **Julia K. Kofler**[c], **William E. Klunk**[a,b], **Oscar L. Lopez**[a,b], **Peter Penzes**[d,e], and **Robert A. Sweet**[a,b,f,*]

[a]Department of Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA, United States

[b]Department of Neurology, University of Pittsburgh School of Medicine, Pittsburgh, PA, United States

[c]Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, PA, United States

[d]Department of Physiology, Northwestern University Feinberg School of Medicine, Chicago, IL, United States

[e]Department of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, United States

[f]VISN 4 Mental Illness Research, Education and Clinical Center, VA Pittsburgh Healthcare System, Pittsburgh, PA, United States

[g]Geriatric Research Educational and Clinical Center, VA Pittsburgh Healthcare System, Pittsburgh, PA, United States

Abstract

Psychosis in Alzheimer disease differentiates a subgroup with more rapid decline, is heritable, and aggregates within families, suggesting a distinct neurobiology. Evidence indicates that greater impairments of cerebral cortical synapses, particularly in dorsolateral prefrontal cortex, may contribute to the pathogenesis of psychosis in AD phenotype. Soluble β-amyloid induces loss of dendritic spine synapses through impairment of long term potentiation. In contrast, the Rho GEF kalirin is an essential mediator of spine maintenance and growth in cerebral cortex. We therefore hypothesized that psychosis in AD would be associated with increased soluble β-amyloid and reduced expression of kalirin in the cortex. We tested this hypothesis in postmortem cortical gray matter extracts from fifty-two AD subjects with and without psychosis. In subjects with psychosis, the β-amyloid$_{1-42}$/β-amyloid$_{1-40}$ ratio was increased, due primarily to reduced soluble β-amyloid$_{1-40}$, and kalirin-7, -9, and -12 were reduced. These findings suggest that increased cortical β-amyloid$_{1-42}$/β-amyloid$_{1-40}$ ratio and decreased kalirin expression may both contribute to the pathogenesis of psychosis in AD.

*corresponding author: Biomedical Science Tower, W1645, 3811 O'Hara St., Pittsburgh, PA 15213, sweetra@upmc.edu, p. 412-383-8548 f.412-624-9910.

Keywords

β-amyloid; kalirin; psychosis; Alzheimer disease

1. Introduction

The emergence of psychosis in individuals with late-onset Alzheimer disease (AD) is an indicator of a more severely progressive form of the disease. Psychotic symptoms, delusions and hallucinations, are frequent in AD, with a prevalence of upwards of 40% (Ropacki and Jeste, 2005). Individuals with AD and psychosis (AD+P) decline more rapidly on measures of cognition and function, and are more likely to be institutionalized (Lopez et al., 1999, Scarmeas et al., 2005). AD+P demonstrates familial aggregation (Sweet et al., 2010, Sweet et al., 2002a), and the estimated heritability of any occurrence of psychotic symptoms in AD is 30%, increasing to 61% for multiple/recurrent symptoms (Bacanu et al., 2005). The familial and heritable nature of AD+P strongly suggests that it develops from a distinct neurobiological origin.

Findings from neuroimaging studies and postmortem studies have pointed to increased synaptic disruption in the neocortex, but not medial temporal cortex, as underpinning the development of psychosis in AD. Structural assessment with magnetic resonance imaging identified reduced gray matter density in frontal and parietal gyri in AD+P subjects in comparison to AD subjects without psychosis (AD-P) (Bruen et al., 2008). Studies of cerebral perfusion with single photon emission computed tomography show hypoperfusion of frontal and parietal lobes (Kotrla et al., 1995), frontal regions (Staff et al., 1999), and dorsolateral frontal and parietal regions (Mega et al., 2000) in AD+P versus AD-P. A positron emission tomography study identified hypometabolism in the frontal lobe of AD+P subjects, compared to AD-P (Sultzer et al., 1995). A magnetic resonance spectroscopy study of synaptic disruption in postmortem tissue identified an excess of membrane breakdown products in several neocortical regions, including the dorsolateral prefrontal cortex (DLPFC), in AD+P (Sweet et al., 2002b). These findings indicate that AD+P is associated with deficits across multiple neocortical regions, however evidence consistently points to frontal regions and the DLPFC in particular.

Evidence of greater neocortical synaptic impairments in AD+P subjects is also consistent with clinical observations that these individuals exhibit a steeper trajectory of cognitive decline than individuals with AD-P (Emanuel et al., 2011, Paulsen et al., 2000, Scarmeas et al., 2005). Loss of synapses is the most robust correlate of degree of cognitive impairment among AD subjects (DeKosky and Scheff, 1990, Scheff and Price, 2006, Terry et al., 1991, Walsh and Selkoe, 2004). The non-specific presynaptic protein synaptophysin, and the intracortical excitatory bouton selective protein vesicular glutamate transporter VGLUT1, are both reduced in AD neocortex and correlated with cognitive decline (Counts et al., 2006, Kashani et al., 2008, Terry et al., 1991). Similarly, dendritic spines, the postsynaptic components of the majority of synapses in the cortex (Rakic et al., 1986), and the dendritic spine associated proteins synaptopodin and drebrin, are reduced in neocortex of subjects with AD, and correlated with cognitive impairment (Counts et al., 2006, Grutzendler et al., 2007, Reddy et al., 2005).

Soluble Aβ oligomers have emerged as the most likely cause of dendritic spine deficits observed in AD. Normally, enhanced synaptic efficacy, dendritic spine enlargement, and spine persistence are correlated phenomena mediated by long-term potentiation (LTP) (Matsuzaki, 2007). Soluble, oligomeric Aβ isolated from AD brains inhibits LTP and induces spine loss (and as a consequence the synapses onto them) in rodent hippocampus,

while insoluble plaque cores do not have the same effects unless solubilized first (Shankar et al., 2008). Studies of transgenic mouse models of AD have demonstrated that well before plaque deposition, increased soluble (non-fibrilllar) Aβ concentration is associated with changes in dendritic length and shape (Wu et al., 2004), reductions in synaptic density (Mucke et al., 2000), and impaired synaptic transmission (Hsia et al., 1999). Application of naturally secreted Aβ oligomers inhibits hippocampal LTP *in vivo* (Walsh et al., 2002) and *in vitro* (Wang et al., 2002), and induces dendritic spine loss *in vitro* (Shankar et al., 2007).

The excess synaptic disruption in AD+P could be driven simply by increased concentrations of soluble Aβ leading to greater inhibition of LTP and resultant spine loss. Alternatively, reductions in proteins which serve to mediate the effects of LTP on dendritic spines could independently lead to excess spine and synapse loss in AD+P. One such mediator is kalirin, a GDP/GTP exchange factor (GEF) which activates the Rho family of GTP binding proteins (Alam et al., 1997, Cerione and Zheng, 1996). Four major isoforms generated through alternative splicing of the kalirin gene are expressed in adult CNS (kalirin-5, -7, -9, -12) (Johnson et al., 2000). In the cortex, kalirin is necessary for LTP-induced dendritic spine enlargement and controls expression of AMPA receptors at the synapse (Xie et al., 2007). In the hippocampus however, other GEFs that are not highly expressed in the cortex may substitute for kalirin, as kalirin knockout mice have reduced dendritic spine densities in the cortex but not hippocampus (Cahill et al., 2009). Kalirin mRNA and protein expression is lower in AD hippocampus compared to cognitively normal controls (Youn et al., 2007a, Youn et al., 2007b). However, kalirin expression in the neocortex of AD subjects, and in relationship to psychosis status of AD subjects, has not been evaluated. Considering the integral function kalirin has in activity-dependent mechanisms of spine enlargement and glutamatergic transmission, reduction in kalirin could play a role in rendering synapses to be more vulnerable in AD+P.

We therefore undertook to evaluate soluble Aβ and kalirin expression in the cerebral cortex of subjects with AD+P in comparison to AD-P subjects. We hypothesized that susceptibility to AD+P may result from a deficit in kalirin, from an increase in Aβ, or their combined effect; more Aβ drive acting on vulnerable synapses may lead to greater loss of synapses in AD+P.

2. Method

2.1. Subjects

Fifty-two subjects (Table 1) underwent neurologic, neuropsychologic, and psychiatric diagnostic evaluations at successive time points as part of their participation in the Clinical Core of the Alzheimer Disease Research Center (ADRC), with methods previously described (Sweet et al., 2001, Sweet et al., 2000).

The presence or absence of delusions and hallucinations were indicated as part of semi-structured examinations conducted by research psychiatrists and rated on the CERAD Behavioral Rating Scale (Tariot et al., 1995). Delusions were defined as a false belief, not attributable to membership in a social or cultural group, based on incorrect inference about external reality. Hallucinations were defined as sensory perceptions for which there was no basis in reality. Psychosis was defined as the presence of any hallucination or delusion. No patient had a history of schizophrenia, schizoaffective disorder, or other idiopathic psychosis.

Diagnosis of definite AD was made at the time of postmortem exam through regional sampling and semiquantitative scoring of neuritic plaques and neurofibrillary tangles, per CERAD diagnostic criteria and neuropathology protocol (Mirra et al., 1991). This procedure

has been described in detail elsewhere (Sweet et al., 2000, Sweet et al., 2002b). The presence or absence of any α-synuclein aggregates was rated as positive or negative, respectively. Semiquantitative rating of cerebral amyloid angiopathy (CAA) severity was also assessed at autopsy (Sweet et al., 2004). Dates of death ranged from November, 1999 to December, 2003.

All samples were obtained through the brain tissue bank of the ADRC at the University of Pittsburgh. At the time of brain removal, postmortem interval (PMI) was recorded and the brain was divided in the midsagittal plane. A series of gray matter samples were dissected from the superior frontal gyrus (DLPFC), inferior parietal cortex (IP), superior temporal gyrus (STG) and occipital cortex (OC) at autopsy and frozen at −80°C.

2.2. Measurement of Soluble Aβ by an ELISA

Gray matter samples from the DLPFC, STG, IP, and OC were homogenized on ice in phosphate-buffered saline (PBS; 150 mg/mL) and rehomogenized in tissue homogenization buffer (250 mM sucrose, 20 mM Tris base, and 10 μL/mL Sigma P8340 protease inhibitor cocktail [Sigma-Aldrich, St. Louis, Missouri, USA]). $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ peptide concentrations were quantified in diethylamine (DEA)-soluble Aβ fractions as described previously (Ikonomovic et al., 2008). The DEA-soluble fraction was prepared by centrifuging the homogenate aliquot at 135,000 × g at 4°C for 1 hour and neutralizing the supernatant with 0.5 M Tris-Cl. The Aβ concentrations were assayed using a colorimetric TMB-based ELISA (Invitrogen, Carlsbad, California) read at 450 nm, with a capture antibody specific for the NH_2 terminus of human Aβ (amino acids 1–16) and detection antibodies specific for the neoepitope at either the 40- or the 42-amino acid end of Aβ. Values were determined from standard curves using synthetic Aβ peptide (Invitrogen, Carlsbad, California) and are expressed as picomoles per gram wet brain tissue.

2.3. Western blot anaylsis of kalirin protein levels

Samples from one AD+P and one AD-P subject were not available to be included in the kalirin assay, resulting in a final N of 50 subjects. To minimize any effects of interassay variability on our primary comparison of AD+P and AD-P subjects, subjects were grouped into sets of four (“quads”), stratified on psychosis presence. Within quads subjects were matched to the extent possible on age and Braak staging (Braak and Braak, 1991). Gray matter from DLPFC tissue samples was homogenized and sonicated in ice cold SDS extraction buffer (0.125 M Tris-HCl (pH 7), 2% SDS, and 10% glycerol), followed by centrifugation at 16,100 g for 10 minutes. Total protein was extracted using SDS extraction buffer at 70°C. Protein concentration was estimated using a bicinchoninic acid assay (BCA™ Protein Assay Pierce # 23225). Quads were run together and assayed in triplicate. The final protein concentration utilized for each sample was the mean of the triplicate runs.

Two quads were examined per run, and each run consisted of 4 gels. Protein (25 μg) was aliquoted in 1x LI-COR Protein Loading Buffer (Li-Cor #928-40004 Licor Inc. Lincoln, Nebraska, USA), loaded on 4–20% SDS-PAGE gradient gels (Thermo Scientific #26224 Thermo Scientific, Rockford, Illinois, USA), and separated for 2 hours at room temperature in 1X SDS running buffer (Pierce 20X Tris Hepes SDS Buffer #28368) at 75 V. Samples were then transferred to polyvinylidene fluoride membranes (PVDF; Millipore Immobilon-FL PVDF #PFL00010) in 1x Tris Glycine Blotting Buffer (Pierce #28363) at 85 V, for 50 minutes at 4°C. Membranes were incubated for 1 hour in Odyssey LiCor Blocking Buffer (LiCor #927-4000) diluted 1:1 in 1x TBS. The membrane was incubated overnight in primary antibodies directed against the spectrin domain of kalirin (rabbit anti-kalirin spectrin, Millipore # 07-122) diluted 1:500, mouse anti-β-tubulin (Millipore #05-661) diluted 1:30,000, in Pierce SuperBlock blocking buffer (Pierce #37353) with 0.1% Tween

20 (Sigma # P7949 Sigma-Aldrich, St. Louis, Missouri, USA). Specificity of the kalirin antibody is shown in Supplemental Figure 1. Membranes were then incubated in LiCor IRDye secondary antibodies (Li-Cor: goat anti-rabbit 800 nm #926-32211; goat anti-mouse 680 nm #926-68020) 1:10,000 in Odyssey Licor Blocking Buffer (Li-Cor # 927-4000) diluted 1:1 with TBS (0.1% Tween 20 + 0.02% SDS). Blots were scanned while wet and bands detected using a Li-Cor Odyssey Infrared Scanner set at a resolution of 42 μm and the highest image quality. Images were quantified using MCID Core Version 7.0 (InterFocus Imaging Ltd., Linton, Cambridge, UK). The peak for each of the 4 isoforms of kalirin and β-tubulin on the output histograms were independently aligned to a single point on the distance axis for all lanes from all blots. Once aligned, a band definition encompassing the full range of each band was applied to all lanes from all blots in the study on the histogram for each protein Supplemental Figure 2. The integrated intensity (mean intensity × number of pixels) was acquired for each protein.

2.4. Statistical Analysis

Demographic, clinical, and pathology variables were compared between groups using chi square tests, ANOVAs, and t-tests where appropriate. When employing linear models and analysis of variance, which are based on the normal distribution, the natural logarithm transformation is standardly used with non-normally distributed data. Although diagnosis groups and quads were matched as closely as possible, they could not be matched perfectly; therefore, potentially relevant biologic variables were included as covariates in all models because they may explain some variation.

2.4.1. Soluble Aβ—The response variable for soluble Aβ analyses was the natural logarithm of the concentration values (pmol/g tissue) for $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$. Since the regions were within subjects, the response variables were initially treated as repeated measures. A repeated measures analysis of covariance (RM-ANCOVA) was used to evaluate group differences, with sex, age, PMI, α-synuclein positivity, and Braak stage included as covariates. The numbers of tissue samples with detectable protein levels were not equal across regions, so RM-ANCOVAs did not include data points from subjects that were missing data in any of the regions. To further clarify the regional differences and to incorporate the additional data, follow-up ANCOVA analyses were performed on the regions individually.

2.4.2. Kalirin—Analyses for the expression amounts of kalirin-5, kalirin-7, kalirin-9, and kalirin-12 were conducted independently. The response variable for each of the analyses was the natural logarithm of the ratio of each kalirin isoform expression level to the corresponding expression level of β-tubulin, which did not differ between groups ($F_{1,\ 30.001} = 0.432$, $p = 0.516$). Four measurements of this ratio were made for each isoform, within each subject (runs with gel artifacts were excluded). Linear mixed models were used for the analyses, with fixed effects as follows: psychotic or not psychotic, sex, age, PMI, Braak stage, and assay run. $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ protein concentrations from the DLPFC were also included as fixed effects.

Secondary models were developed including data from a reference group of 4 neuropathologically normal control subjects (3 male, 1 female; 76 ± 14.5 years of age; 4.3 ± 0.5 hours PMI) included to provide directional information for our primary analyses rather than for hypothesis testing.

All tests were two-tailed with $\alpha = 0.05$.

3. Results

AD+P and AD-P did not differ with regard to sex (χ^2_1=0.227, p = 0.634), α-synuclein score (χ^2_2=1.023, p = 0.600), neuritic plaque rating (χ^2_2=3.237, p = 0.356), or Braak score (χ^2_2=3.412, p = 0.332). The groups also did not differ with regard to age ($F_{1, 50}$ = 0.007, p = 0.936) or PMI ($F_{1, 50}$ = 1.933, p = 0.171).

3.1 Soluble Aβ

3.1.1. Aβ$_{1-40}$—Concentrations of Aβ$_{1-40}$ were lower in AD+P subjects (Figure 1a, $F_{1, 12}$ = 8.426, p = 0.013). Aβ$_{1-40}$ concentrations were not influenced by age (p = 0.614), sex (p = 0.083), PMI (p = 0.743), Braak stage (p = 0.465), or α-synuclein positivity (p = 0.738). Analyses of individual regions found that Aβ$_{1-40}$ concentrations were reduced by 50% in the DLPFC ($F_{1, 45}$ = 9.770, p = 0.003), 39% in OC ($F_{1, 47}$ = 5.394, p = 0.025), 84% in STG ($F_{1, 25}$ = 5.185, p = 0.032), and were nearly significantly lower in the IP (69%, $F_{1, 49}$ = 3.903, p = 0.054).

Since Aβ$_{1-40}$ is the predominant species in vascular amyloid deposits (Joachim et al., 1988, Suzuki et al., 1994), we compared CAA ratings (none, mild, moderate, severe) between AD+P and AD-P. CAA ratings did not differ between the groups, χ^2_2=5.420, p = 0.144.

3.1.2. Aβ$_{1-42}$—Concentrations of Aβ$_{1-42}$ were not significantly different between AD+P and AD-P subjects (Figure 1b, $F_{1, 13}$ = 1.479, p = 0.245). Aβ$_{1-42}$ concentrations were not influenced by age (p = 0.427), sex (p = 0.289), PMI (p = 0.820), Braak stage (p = 0.358), or α-synuclein positivity (p = 0.963). Individual analyses verified that AD+P and AD-P groups had comparable levels of Aβ$_{1-42}$concentration in the IP ($F_{1, 48}$ = 1.253, p = 0.269), DLPFC ($F_{1, 47}$ = 0.391, p = 0.535), OC ($F_{1, 46}$ = 2.349, p = 0.132), or STG ($F_{1, 25}$ = 1.867, p = 0.184).

3.1.3. Aβ$_{1-42}$/Aβ$_{1-40}$ Ratio—The ratios of Aβ$_{1-42}$/Aβ$_{1-40}$ were nearly significantly different between AD+P and AD-P (Figure 1c, $F_{1, 12}$ = 4.396, p = 0.058) in the repeated measures analysis. Ratios were not influenced by age (p = 0.654), sex (p = 0.111), PMI (p = 0.812), α-synuclein positivity (p = 0.854), or Braak stage (p = 0.181). Individual analyses found that the ratio was significantly higher in AD+P DLPFC ($F_{1, 44}$ = 9.123, p = 0.004), though not in the IP ($F_{1, 48}$ = 1.364, p = 0.249), the OC ($F_{1, 46}$ = 1.509, p = 0.226), or the STG ($F_{1, 25}$ = 0.768, p = 0.389).

3.2 Kalirin isoform expression in the DLPFC

3.2.1. Kalirin-5—Kalirin expression levels are presented in Figure 2. Kalirin-5 was not significantly changed in AD+P subjects ($F_{1, 28.120}$ = 0.365, p = 0.550). Expression was not influenced by age (p = 0.353), sex (p = 0.575), PMI (p = 0.591), Braak stage (p = 0.23), Aβ$_{1-40}$ concentration (p = 0.308), or Aβ$_{1-42}$ concentration (p = 0.549).

3.2.2. Kalirin-7—Kalirin-7 was significantly lower in AD+P subjects (11.6%, $F_{1, 27.758}$ = 6.963, p = 0.013). Expression was not influenced by sex (p = 0.223), PMI (p = 0.785), Aβ$_{1-40}$ concentration (p = 0.710), or Aβ$_{1-42}$ concentration (p = 0.253). Age (p = 0.024, Supplemental Figure 3) and Braak stage (p = 0.023, Supplemental Figure 4) did have significant effects, with a slight increase with increasing age and a decrease with increasing Braak score.

3.2.3. Kalirin-9—Kalirin-9 was significantly lower in AD+P subjects (12.1%, $F_{1, 21.588}$ = 5.923, p = 0.024). Sex (p = 0.946), PMI (p = 0.735), Braak stage (p = 0.197), Aβ$_{1-40}$

concentration ($p = 0.339$), and $A\beta_{1-42}$ ($p = 0.439$) did not have significant effects. Age had a nearly significant effect ($p = 0.056$), showing a slight increase with increasing age.

3.2.4. Kalirin-12—Kalirin-12 was significantly lower in AD+P subjects (17.8%, $F_{1, 27.056} = 6.516$, $p = 0.017$). Sex ($p = 0.985$), PMI ($p = 0.953$), Braak stage ($p = 0.108$), $A\beta_{1-40}$ concentration ($p = 0.304$), and $A\beta_{1-42}$ ($p = 0.502$) did not produce significant effects. Effect of age was significant ($p = 0.012$), with a slight increase with increasing age.

4. Discussion

In the present study, we explored a model of AD pathology and synaptic vulnerability in AD +P. We found an increased ratio of $A\beta_{1-42}/A\beta_{1-40}$ in the DLPFC in AD+P, driven largely by reduced concentrations of $A\beta_{1-40}$ peptide. Although we identified a significantly increased ratio only in the DLPFC in our study, we did detect lower $A\beta_{1-40}$ across the regions we studied, and a nonsignificant increase in the $A\beta_{1-42}/A\beta_{1-40}$ ratio in these regions (Figure 1c). In addition to these findings, we found that kalirin-7, -9, and -12 isoforms were also expressed at lower levels in the DLPFC in AD+P.

4.1 Lower $A\beta_{1-40}$ may enhance the toxicity of $A\beta_{1-42}$

Emerging data is illuminating the relative contributions of soluble $A\beta_{1-40}$ and $A\beta_{1-42}$ to synaptic pathology in AD. Although $A\beta_{1-40}$ has been shown to produce harmful effects *in vitro* and *in vivo*, and it has been shown that, similar to $A\beta_{1-42}$ species, increased concentrations of $A\beta_{1-40}$ forms correlate with impaired cognition (Näslund et al., 2000) in the same brain regions examined in the present study. However $A\beta_{1-40}$ forms do not produce insoluble fibrils as readily as $A\beta_{1-42}$, and this peptide is not as potent a synaptotoxin as $A\beta_{1-42}$. Recent studies indicate that $A\beta_{1-40}$ may even serve to ameliorate the effects of $A\beta_{1-42}$. PSD-95 protein was reduced in cell culture after application of both $A\beta_{1-40}$ (Roselli et al., 2005) and $A\beta_{1-42}$ (Almeida et al., 2005). ICV-administered $A\beta_{1-40}$ reduced the duration of LTP over time in the rat hippocampus (Cullen et al., 1997); however, $A\beta_{1-42}$ had a comparable effect at only 2.5% of the $A\beta_{1-40}$ concentration (0.01 nM vs 0.4 nM). $A\beta_{1-40}$ has been shown to inhibit the oligomerization of $A\beta_{1-42}$ into more toxic species by sequestering it into stable mixed tetramers (Murray et al., 2009). In the Swedish APP mutation mouse model, an increased $A\beta_{1-42}/A\beta_{1-40}$ ratio was identified in conjunction with impairments in LTP and reduced hippocampal spine density, before overt plaque deposition or increase in overall amyloid levels (Jacobsen et al., 2006). Conversely, increased expression of $A\beta_{1-40}$ relative to $A\beta_{1-42}$ abolished the premature death rate normally observed in $A\beta_{1-42}$-overexpressing transgenic mice (Kim et al., 2007). Taken as a whole, these data suggest that the net effect of lower $A\beta_{1-40}$ and an increased ratio of $A\beta_{1-42}/A\beta_{1-40}$ in the DLPFC may be overall enhancement of Aβ toxicity in AD+P. This is consistent with the observations by Kuperstein and colleagues (2010) who reported that the $A\beta_{1-42}/A\beta_{1-40}$ ratio is more critical for neurotoxicity compared to the individual peptide concentration, and that even slight increases in this ratio promote synaptotoxic oligomer species (Kuperstein et al., 2010).

Increasing evidence indicates that it is soluble and not insoluble forms of Aβ that primarily contribute to synapse impairment and loss in AD (Selkoe, 2002) and that plaques composed of insoluble Aβ may serve as deposits or reservoirs of soluble oligomers (Koffie et al., 2009). However, several lines of evidence indicate that our findings of reduced soluble $A\beta_{1-40}$ do not simply result as an artifact of increased aggregation into plaques. First, the individuals in our cohort all had similarly high plaque burdens. Additionally, it is $A\beta_{1-42}$, not $A\beta_{1-40}$, that is the principal alloform present in plaques (Gravina et al., 1995). Finally, previous studies have not identified an association between psychosis in AD and Aβ plaque pathology (Farber et al., 2000, Sweet et al., 2000).

4.2 Lower kalirin may confer a synaptic vulnerability in AD+P

Our findings that kalirin-7, -9, and -12 proteins are lower in AD+P than in AD-P subjects are consistent with the interpretation of an increased synaptic vulnerability and subsequent synaptotoxicity in AD+P. An important question is whether kalirin downregulation is a consequence of Aβ-driven synapse loss, or contributes separately to synaptic pathology in AD+P. We found reductions in kalirin-7, kalirin-9, and kalirin-12 in our subjects, but not in kalirin-5. Kalirin isoforms are present in post-synaptic density fractions of rodent and human cortex (Deo et al., 2011, Penzes et al., 2000); thus, the relative preservation of kalirin-5 in our AD+P subjects suggests that lower kalirin-7, kalirin-9, and kalirin-12 is unlikely to be due to confounding by greater spine loss in AD+P. Similarly, the reductions in expression of kalirin-7, kalirin-9, and kalirin-12 persisted after controlling for Aβ concentrations in our analyses, suggesting they did not arise solely as a consequence of Aβ toxicity, but rather may make independent pathogenic contributions to this deficit.

Kalirin plays an integral role in dendritic spine growth, morphogenesis, and activity-dependent plasticity. NMDA receptor activation leads to kalirin-7 phosphorylation, which is necessary for activity-dependent spine targeting of AMPA receptors and Rac1-dependent spine enlargement (Xie et al., 2007). A Rac1 substrate, p21-activated kinases (PAK), is critical to regulation of actin assembly in dendritic spines (Penzes et al., 2003, Zhao et al., 2006), implicating a direct downstream effect of reduced kalirin on cytoskeleton remodeling in spines (Penzes et al., 2011, Penzes and VanLeeuwen, 2011). Both kalirin-9 and kalirin-12 are involved in dendritic development (May et al., 2002), although the functions of kalirin-9 and kalirin-12 in synaptic signaling and the structural integrity of dendritic spines are still unclear. Kalirin KO mice, in which all kalirin species are eliminated, have reduced cortical spine density, impaired glutamatergic transmission, and associated working memory deficits (Cahill et al., 2009). $A\beta_{1\text{-}42}$ oligomer-mediated dendritic spine loss occurs, at least in part, in an NMDA receptor-dependent manner (Shankar et al., 2007). It is thus plausible that the deleterious effects of Aβ on dendritic spines, coupled with a synaptic vulnerability conferred by less kalirin, may produce additive or synergistic synaptotoxic effects in AD+P.

A significant strength of this study was our cohort of subjects. The individuals were followed and evaluated during the progression of their disease, allowing for an extensive characterization of late-life behavior and cognition with corresponding postmortem analysis. Subjects were matched on a range of variables, including age, illness duration, PMI, Braak stage, and neuritic plaque severity so as to ensure that the identified postmortem correlates of psychosis were not due to having sampled AD+P subjects with more advanced pathologies than AD-P subjects, but rather to a discrete pathogenic process. Importantly, despite matching on these measures, MMSE scores were lower in the AD+P group (t_{50} = 2.418, p = 0.019), indicating a more severe trajectory of decline in the AD+P subjects. Since synapse loss is strongly correlated with cognitive decline in AD (DeKosky and Scheff, 1990, Scheff and Price, 2006, Terry et al., 1991, Walsh and Selkoe, 2004), this finding lends further support to our proposition of kalirin-mediated synaptic vulnerability in AD+P.

Similar to AD+P, presentation of Dementia with Lewy Bodies (DLB) may include the presence of hallucinations and delusions (McKeith et al., 2004). Though our cohort excluded individuals with isolated DLB, our subjects were matched on the presence or absence of α-synuclein aggregates to control for any potential contribution of comorbid DLB pathology in these AD cases. However, since this was an examination of postmortem tissue, it was impossible to account for all possible variables that may have influenced the findings. We corrected for the strongest and most obvious influences, such as the variables just mentioned both through subject groupings and in the statistical analyses.

5. Conclusion

We found reduced concentrations of soluble $A\beta_{1-40}$, an increased ratio of soluble $A\beta_{1-42}$/$A\beta_{1-40}$ and reduced kalirin-7, -9, and -12 protein expression in AD+P. These findings suggest that decreased $A\beta_{1-40}$ may be an underlying factor in the development of psychosis in AD. Lower $A\beta_{1-40}$ may serve to enhance the deleterious effects of $A\beta_{1-42}$, promoting the dendritic spine loss that is exaggerated in AD+P. Lower kalirin expression may further enhance this effect, with spines more sensitive to Aβ and less responsive to activity-dependent maintenance and growth. While our study did not directly establish a link between soluble Aβ and kalirin, we did describe a profile of protein expression in a large cohort of AD subjects with and without psychosis that were matched on a series of demographic, clinical, and pathologic variables. These findings provide a foundation for identifying a novel pathway in the pathogenesis of AD+P; an increased $A\beta_{1-42}/A\beta_{1-40}$ ratio driven by lower $A\beta_{1-40}$, coupled with reduced kalirin, isolates additive and potentially related processes that may underlie the enhanced synaptic disruption in AD+P.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

AD	Alzheimer disease
AD+P	Alzheimer disease with psychosis
AD-P	Alzheimer disease without psychosis
DLPFC	dorsolateral prefrontal cortex
Aβ	β-amyloid
LTP	long-term potentiation
CAA	cerebral amyloid angiopathy
PMI	postmortem interval
SF	superior frontal gyrus
IP	inferior parietal cortex
STG	superior temporal gyrus
OC	occipital cortex

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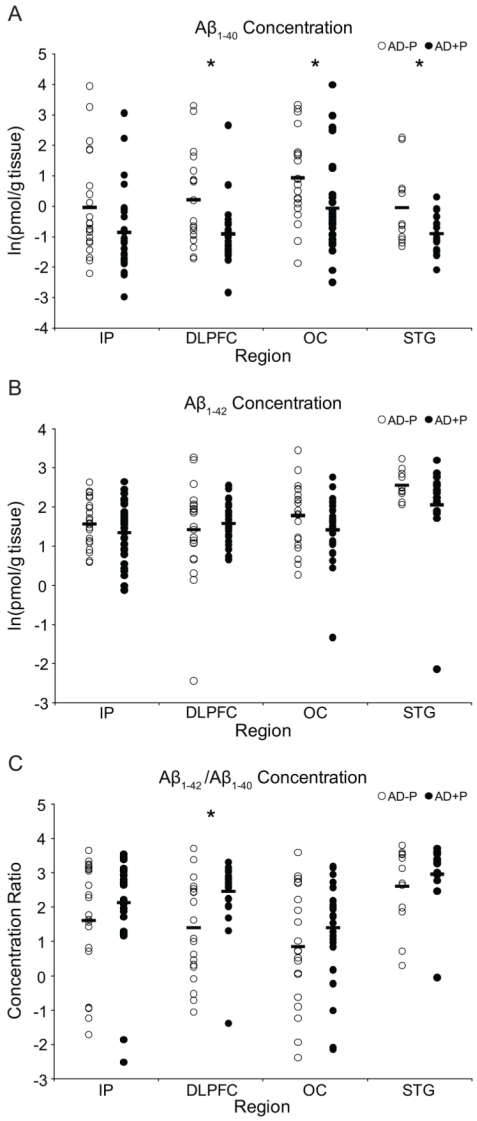

Figure 1.

a. Log-transformed concentrations of $A\beta_{1\text{-}40}$ in the inferior parietal cortex (IP), superior frontal gyrus (DLPFC), occipital cortex (OC), and superior temporal gyrus (STG). b. Log-transformed concentrations of $A\beta_{1\text{-}42}$ in the IP, DLPFC, OC, and STG. c. Log transformations of the concentration ratios of $A\beta_{1\text{-}42}$ and $A\beta_{1\text{-}40}$ in the IP, DLPFC, OC, and STG. Markers represent values or ratios for individual subjects; horizontal bars represent mean values or ratios for each group. * indicates $p < 0.05$.

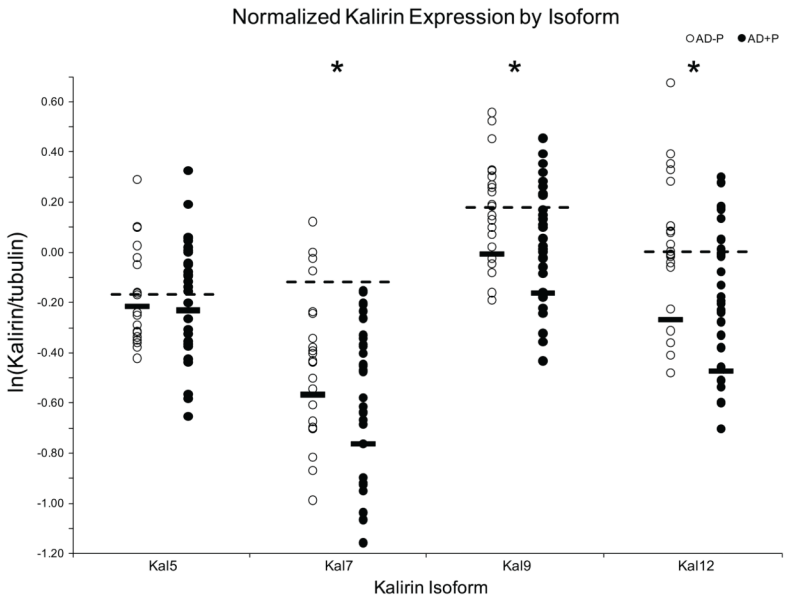

Figure 2.

Log-transformed normalized expression of Kalirin isoforms in the superior frontal gyrus (DLPFC). Markers represent mean values for individual subjects; black horizontal bars represent estimated marginal mean values for each group. Dashed lines represent estimated marginal mean values for control subjects. Marginal means are from models not including Aβ. * indicates $p < 0.05$.

Table 1

Descriptive information of the subjects involved in the study.

Variable	AD - P	AD + P	p-value
Age, years	80.6 ± 8.7	80.7 ± 7.9	0.936
Age of onset, years	69.5 ± 9.4	71.0 ± 9.0	0.564
Duration of illness, years	11.0 ± 4.5	9.7 ± 5.0	0.339
Gender			0.634
Male	11 (50)	13 (43)	
Female	11 (50)	17 (57)	
Post mortem interval, hours	4.9 ± 1.6	5.7 ± 2.5	0.171
α-synuclein			0.600
Positive	9 (41)	15 (50)	
Negative	13 (59)	15 (50)	
Braak			0.332
3	4 (18)	1 (3)	
4	3 (14)	4 (13)	
5	4 (18)	8 (27)	
6	11 (50)	17 (57)	

Mean values ± SD or number of subjects with percentage of group in parentheses. Groups did not differ with regard to any of the variables listed.